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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/060,294	JENSEN ET AL.	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77,78 and 80-132* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77,78,80,81,85,87-91,104-106,110,117-122,124,129,131 and 132* is/are rejected.

7)☒ Claim(s) *92-97* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 82-84,86,98-103,107-109,111-116,123,125-128 and 130.

DETAILED ACTION

The amendment filed 06/24/2004 has been entered. Claims 77, 78, 80-132 are pending. Applicant's elected group I in the paper filed 10/21/2003. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicant's elected with traverse the species E/F loop substitution in the paper filed 10/21/2003. The traversal was on the ground(s) that the substitution in the E strand and in the E/F connecting loop species and the substitution in the E strand and in the E/F and D/E connecting loop species should also be examined with the elected species. This was found persuasive. The requirement was still deemed proper and was therefore made FINAL. Claims 82-84, 86, 98-103, 107-109, 111, 115, 116, 123, 125-127, 128, 130 were withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species or invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the paper filed 10/21/2003.

The application is not fully in compliance the sequence rules, 37 C.F.R. § 1.821-1.825. The specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. See pages 37, 43, Figures-3a, -3b. This is not meant to be an exhaustive list of places where the specification fails to recite the appropriate sequence identifiers. The application cannot issue until it is in compliance. Nucleic acid sequences with 10 or more nucleotides, at least 4 of which are specifically defined, must comply with the sequence rules. Amino acid sequences with 4 or more residues, at least

4 of which are specifically defined, must comply with the sequence rules. Applicant may bring the Figures into compliance by amending either the Figures or the "Brief Description of the Drawings" to recite the appropriate sequence identifier. Applicants' amendment filed 07/20/00 (Paper No. 13) is noted. However, the sequence listing does not contain a "SEQ ID NO: 339737". Furthermore, the amino acid sequence (Figure 3b) and the nucleotide sequence (Figure 3a) require separate identifiers.

Correction is required.

Claims 77, 78, 80, 81, 85, 87-91, 104-106, 110, 117-122, 124, 129, 131, 132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mouritsen (AV, cited by Applicants) in view of {Pennica (BP, cited by Applicants), Shirai (BN, cited by Applicants), or Wang (BL, cited by Applicants)}, further in view of Jones (BF, cited by Applicants), and further in view of Panina-Bordigon (BO, cited by Applicants).

Applicants argue that Mouritsen does not teach or suggest the possible neutralizing activity of the antibodies, that the rejection relies on teachings allegedly inherent in Mouritsen but that Mouritsen does not mention TNF-neutralizing antibodies, that an argument by the PTO is "not prior art," that both the idea and the means must be present in the prior art to show obviousness, that that none of the secondary references teaches or suggest the desirability of obtaining neutralizing antibodies. Applicant's arguments have been fully considered but they are not persuasive. ,

The examiner relies on Mouritsen for teaching that toxic self proteins such as TNFα can be simultaneously detoxified by removing or mutating biologically active protein segments (page 7, lines 11-15) and that the modified TNFα could be administered

as an anti-TNFα vaccine to patients suffering from diseases where TNFα is important for the pathogenesis (page 14, lines 13-20, 26-30; paragraph bridging pages 14-15). Mouritsen's teaching of a TNF vaccine teaches or suggest to one of ordinary skill in the art to produce neutralizing antibodies. Furthermore, one of ordinary skill in the art knows that highly potent inhibiting and/or neutralizing anti-TNF antibodies are preferred for therapeutic use in TNFα-mediated pathologies or conditions. See Le (U. S. Patent No. 5656272), column 9, lines 45-50; paragraph bridging columns 48-49. One of ordinary skill in the art would be motivated to select a modification of TNFα that gives rise to neutralizing anti-TNFα antibodies because neutralizing anti-TNFα antibodies would be expected to be an effective treatment for TNFα-mediated conditions.

Applicants argue that that it was known at the time of the instant invention that antibodies could be induced that would merely effect clearance of circulating antigen and that the prior art does not teach that clearance-effecting antibodies are insufficient. Applicant's arguments have been fully considered but they are not persuasive. The prior art of record does not teach that clearance-effecting antibodies are sufficient.

Applicants argue that the Mouritsen's TNF2-1 molecule does not provide a neutralizing antibody, that Mouritsen does not test any of the substituted TNF molecules for the ability to induce neutralizing antibodies, and that the examiner is using improper hindsight. Applicant's arguments have been fully considered but they are not persuasive. Mouritsen does not teach a TNF2-1 molecule. Mouritsen does teach a "MR105" modified TNFα molecule, and the present specification teaches that the antibodies induced by Mouritsen's modified TNFα molecules were able to interfere with TNFα and its receptor in vitro as well as in vivo (paragraph bridging pages 35-36).

Applicants argue that the rejection fails to explain how the skilled artisan would have known or expected that such immunogenic molecules could be prepared, that Mouritsen does not specify the means for providing TNF variants that are both non-toxic and capable of inducing neutralizing antibodies, that Mouritsen does not point to any specific parts of murine TNF that would be suitable for substitution.. Applicant's arguments have been fully considered but they are not persuasive. Obviousness does not require absolute predictability, only a reasonable expectation of success, i.e., a reasonable expectation of obtaining similar properties. The prior art of Jones recognizes that there are neutralizing and non-neutralizing TNF-α antibodies. Therefore, one of ordinary skill in the art would have at least a reasonable expectation of obtaining neutralizing antibodies. Furthermore, Mouritsen teaches detoxifying TNFα by removing or mutating biologically active protein segments (page 7, lines 11-15) and that the modified TNFα could be administered as an anti-TNFα vaccine to patients suffering from diseases where TNFα is important for the pathogenesis (page 14, lines 13-20, 26-30; paragraph bridging pages 14-15). These teachings suggest detoxifying TNFα and teaching of a vaccine suggest neutralizing antibodies.

Applicants argue that none of the cited references teaches or suggest the necessity of preserving the β-sheet structure of the B and G strands. Applicant's arguments have been fully considered but they are not persuasive. The examiner construes the limitation "which substitution essentially ensures preservation of the β-sheet structures of the B and G strands" as allowing some substitution of the B and G strands as long as some β-sheet structure remains. it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to select those substitution that produce neutralizing

antibodies. If substitution of the B and G strands does not produce neutralizing antibodies, then one of ordinary skill in the art would be motivated not to use modified TNFα's having substitutions in the B and G strands, thus preserving the β-sheet structures of the B and G strands.

Applicants argue that Jones does not teach or suggest that a substitution in the E/F connecting loop would render the resulting modified TNF immunogenic, detoxify the resulting modified TNF, or render the resulting modified TNF capable of generating neutralizing antibodies. Applicants argue that that Jones does not teach that it is essential to preserve the β-sheet structures of the B and G strands. Applicants argue that if one wishes to raise neutralizing antibodies, following the teachings of Jones one would preserve amino acids 1-15 and/or Arg 131, and that constructs TNF2-4 and TNF30-4 that preserve amino acids 1-15 and 131 are incapable of inducing neutralizing antibodies. Applicants argue that one of ordinary skill in the art would be dissuaded from making changes in the in the highly flexible loop regions because such substitutions would destroy the linear epitopes in the flexible loop regions. Applicants argue that it has not been shown how one of ordinary skill in the art would expect that a modified TNF harboring substitution in the regions of amino acids 84, 86, 87 would be capable of inducing neutralizing antibodies. Applicants argue that Jones does not teach or suggest anything regarding a Modified TNF's ability to induce antibodies against human TNF.

Applicant's arguments have been fully considered but they are not persuasive. Mouritsen clearly teaches that toxic self proteins such as TNFα can be simultaneously detoxified by removing or mutating biologically active protein segments (page 7, lines 11-15) and Jones teaches biologically active protein segments of TNFα. Jones further recognizes

that an antibody binding TNF-α sufficiently close to a putative TNF-α receptor binding site blocks the receptor binding (Jones, paragraph bridging pages 119 and 121). Thus, one of ordinary skill in the art recognizes that a neutralizing antibody does not have to bind a receptor binding site per se. It only has to bind sufficiently close to a putative TNF-α receptor binding site to sterically block receptor binding. Thus, the teachings of Jones are not so restricted as Applicants' arguments would suggest. The obvious choice of one of ordinary skill in the art would be to choose a modified TNFα, wherein the modification simultaneously detoxifies the TNFα and renders the modified TNFα capable of inducing neutralizing antibodies and suitable as an anti-TNFα vaccine, regardless of the particular regions involved in antibody binding. Patentability requires novelty and unobviousness in light of the prior art, not in light of what the inventor knew and included in his patent application.

Conclusion

Claims 92-97 are objected to as being dependent upon a rejected base claim.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the

advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571)272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

BEFORE FINAL (703) 872-9306
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CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (571) 273-0890.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
SEPTEMBER 30, 2004